REMARKS

Claims 18 and 41 have been amended to remove the formal objection stated by the Examiner. It is believed this objection has now been satisfied. Dependent claims 43 and 44 have been added to recite a method of carrying out a bioassay using the biochip of claim 30. It is understood that these claims will stand as withdrawn. However, in accordance with the USPTO pronouncement with respect to the case of *In re Ochiai*, Applicants wish to retain the right for automatic rejoinder of these claims upon the allowance of a product claim. Dependent claims 3 and 32 have been amended so as to specify that the polyethylene glycol, polypropylene glycol or copolymer thereof has a molecular weight of at least about 5000, support for which is found at page 11, line 16. In this respect, Hypol PreMa G-50, which is used in Examples 1, 1a and 2, is believed to be a reaction product of a polyethylene glycol having a molecular weight of about 5500.

Independent claims 1 and 31 define an invention that would not be anticipated by the disclosure of U.S. Patent No. 4,098,645 to Hartdegen et al. (hereinafter Hartdegen et al.). Claims 1 and 31 have been amended to recite a biochip having a plurality of optically clear hydrogel cells attached to the surface of a solid substrate at discrete locations in an array with different binding entities immobilized within or upon different hydrogel cells. Hartdegen et al. is not concerned with a biochip, but it is instead concerned with creating a rigid foam wherein a protein, particularly an enzyme, is immobilized. The rigid foam is either packed into a column (Example 1), or cut into small pieces (Example 13) for use in batch processing. In creating the foamed product, the enzyme is mixed with a low molecular weight prepolymer (preferably about 1000) and then water is admixed to produce a porous, open-cell foam wherein the enzyme will be immobilized. The foam is either then physically packed into the interior of a column

through which a solution of material can be passed on which the enzyme can then react, or cut into blocks for use in batch processing.

Hartdegen et al. are in no way concerned with producing a tool useful in a bioassay where, on a solid surface, there are a plurality of discrete cells or spots which include different binding entities. It was originally acknowledged, on page 6, lines 10-21 of the present application, that U.S. Pat. No. 4,098,645 to Hartdegen et al. taught the creation of enzyme reactors and antibody/antigen based affinity columns by using isocyanate-capped liquid polyurethane prepolymers to directly react with proteins to immobilize proteins within rigid polyurethane foams. The processes Hartdegen et al. taught do not form optically clear hydrogels of controlled geometry which would be suitable for biochip use. Foam is the antithesis of the optical clarity for which Applicants strive (see page 17, lines 14-18), where steps are described by which Applicants positively avoid the creation of foam. The Hartdegen et al. methods use a low molecular weight prepolymer (based on polyols of about 1000-see column 16, lines 5-6) to formulate an aqueous composition that is 33 weight percent or higher polymer (see Examples 2 and 10 and column 13, line 16) to produce the desired rigid, self-supporting foam (column 6, line 50). In contrast, Applicants preferably use about 3.5 weight percent of a substantially higher molecular weight prepolymer and control conditions to avoid foaming. The open-cell foam that Hartdegen et al. create would be of no use in any optical detection application.

Claims 1 and 18 have been amended to specify the details of the biochip wherein a plurality of three-dimensional hydrogel cells are bound to the top surface of a substrate at discrete locations in an array. For the above reasons, it is submitted that it is clear that claims 1 and 31, as amended, would clearly not be anticipated by the disclosure of

Hartdegen et al. Moreover, dependent claims 3 and 32 have been amended to specify that the polyethylene glycol, polypropylene glycol or a copolymer thereof has a molecular weight of at least about 5000 (support for which is found at page 11, line 16), which further distinguishes Applicants' optically clear hydrogel cells from the foam product made using the relatively low molecular weight polyol of Hartdegen et al. – see Procedures 6 and 8 in column 22, e.g. PEG 1000.

Independent claims 1, 18, 31 and 41 define an invention that is not anticipated by the disclosure of U.S. Patent No. 5,624,711 to Sundberg et al (hereinafter Sundberg et al.). Sundberg et al. is, of course, directed to a biochip that utilizes a solid surface, such as a glass slide, and does have a plurality of localized areas which respectively carry diverse polymeric probes; however, it is there any similarity ends. Sundberg et al. utilize an overall coating which covers the entire surface and are not concerned in any way with hydrogels. The word "hydrogel" is absent from the 28 columns of description and claims in the Sundberg et al. patent. The polymer coating is applied as a film that covers the entire surface, as by dip-coating, see column 15, lines 35-52. Clearly there is no teaching of the creating of a plurality of discrete hydrogel cells; thus, there is no anticipation.

Independent claims 1 and 18 define an invention that would not be obvious from the disclosure of U.S. Patent No. 6,406,921 to Wagner et al. (hereinafter Wagner et al.) in combination with the disclosure of Hartdegen et al. For the reasons set forth hereinbefore, Hartdegen et al. do not teach the use of a plurality of discrete cells of an optically clear hydrogel. It is submitted that there would be no impetus, other than in hindsight, to suggest combining the Hartdegen et al. technique of immobilizing enzymes in a polymeric rigid, open-cell foam to be packed into a column and then used to

chemically treat solutes in a solution being caused to flow through that column, with the protein biochip described by Wagner et al.

Wagner et al. do teach a protein biochip where different proteins are respectively attached at discrete regions of an array, as do Applicants; however, it is there that the similarity ends. Wagner et al. optionally coat the substrate in the regions that will become the protein patches, with an intermediate coating, e.g. vapor-deposited aluminum or silicon dioxide, and then with a "self-assembling monolayer." As defined at column 5, line 56 et seq.; this is a single-molecule thick layer of organic molecules. Examples of such acceptable monolayers are given at column 8, lines 23-31, namely: (i) alkylsiloxanes, (ii) alkyl-thiol/dialkyldisulfides, and (iii) an alkyl monolayer formation on oxide-free passivated silicon. FIG. 4 illustrates such a monolayer in the form of a chain, preferably between 8-22 carbons long having a functional group at the end, i.e. N-hydroxysuccinamide, which will couple to the protein.

As admitted at the bottom of page 8, the Examiner recognizes that Wagner et al. do not use an isocyanate-capped polyurethane prepolymer that would form a hydrogel. In an attempt to alleviate this deficiency in the Wagner et al. disclosure with respect to claims 1 and 18, the Examiner would propose to combine the disclosure of Hartdegen et al. which, as stated above, merely teaches the immobilization of enzymes or other proteins in a rigid, open-cell foam that can then be packed into the interior of a column so the enzymes will process solutes in a feed liquor being caused to flow through such column. For example, invertase bound to the polyurethane foam can be used to convert sucrose to invert sugar, see column 13, lines 26-27. The Examiner's rejection on this combination of references should be reconsidered and withdrawn for two reasons. First, as set forth above, Hartdegen et al. do not teach the use of an optically clear hydrogel that

would be suitable for employment in a biochip or microarray as a discrete three-dimensional cell; the foam taught would not be useful in an optical application. Second, the combination is one based solely on hindsight, and the Examiner has not truly made a prima facie case of why the proposed combination would be appropriate under the law as it has developed with regard to 35 U.S.C. § 103.

The Federal Circuit reiterated the manner in which obviousness rejections are to be reviewed: Where claimed subject matter has been rejected as obvious in view of a combination of prior art references,

> "a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q. 2d 1438, 1442 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988).

The Federal Court has emphasized this by succinctly summarizing as follows: "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the Applicant's disclosure" *Id.*

Contrary to the Examiner's position, neither Wagner et al. nor Hartdegen et al., alone or in combination, suggests doing what the Applicants have done.

In other words, it is settled law that the combination of one reference with another is not proper unless there is some suggestion or motivation to make such a modification – which may not be only in the hindsight of Applicants' disclosure. In this respect, the decision of the CAFC in the case of *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783 (Fed. Cir. 1992) is particularly pertinent:

> "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under § 103, teachings of references can be combined only if there is some suggestion or incentive to do so. ACS *Hosp. Systems, Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). Although couched in terms of combining teachings found in the prior art, the same inquiry must be carried out in the context of a purported obvious 'modification' of the prior art. The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification."

It is submitted that there is simply no suggestion of the desirability of modifying the system of the Wagner et al. reference as the Examiner proposes. The Wagner et al. system is shown in FIG. 4 where the monolayer is depicted as having functional groups Y at the ends that are alleged to be particularly effective. The Wagner et al. patent application was filed in 1998, some 20 years after Hartdegen et al. issued; if anything, the time sequence stands as further evidence that the rigid, open-cell foam described by Hartdegen et al. was not felt to be appropriate for use in a biochip or microarray.

The key proposition, stated in 1984, still remains the law in the United States and is found in a more recent case where the Federal Circuit again stated:

> "...A determination of obviousness must involve more than indiscriminately combining prior art, a motivation or suggestion to combine must exist." *Micro Chemical, Inc. v. Great Plains Chemical Co., Inc.*, 103 F.2d 1538, U.S.P.Q. 2d 1238 (Fed. Cir. 1997).

It is submitted that the Examiner's assertion that one of ordinary skill in the art can find not only suggestion, but also reasonable expectation of success, in this combination simply cannot stand scrutiny. The June 2002 U.S. patent to Wagner et al.,

as is clear from the claims, is directed to an improvement in the attachment of proteins to the surface of a solid substrate as part of a microarray. There is absolutely nothing that would cause one of skill in the art to look to the disclosure of Hartdegen et al. (of some 24 years earlier) for an alternative method of attachment that would be more advantageous.

In view of the fact that there simply is no fair suggestion that would lead one to modify the Wagner et al. reference to use the 20-year old disclosure of Hartdegen et al., it is submitted that the rejection under § 103 can only be made on the basis of hindsight in view of Applicants' own disclosure, which is improper. Therefore, it is submitted that the rejection under § 103 should be reviewed and withdrawn.

The parallel rejection under § 103 of claims 31-35, 37, 41 and 42 over Sundberg et al. in view of Hartdegen et al. is likewise lacking in a prima facie case of obviousness based upon the analysis set forth immediately hereinbefore. Sundberg et al. utilizes an overall coating which covers the entire surface which creates localized areas that are clearly two-dimensional. To substitute an overall layer of foam which is three-dimensional and not optically clear would in no way be suggested by either of these references. Although Sundberg et al. mention that the surface could have wells, trenches, flow-through regions, etc., there is nothing discrete about the polymeric coating; it is an overall film. It can be provided by dip-coating, see column 15, lines 35-39, into a solution of the polymer in an organic solvent that is then evaporated, or it can be dipped in a mixture which contains monomers plus an initiator in a solvent, see column 16, line 18. Thus, neither of these references teaches the claimed combination of a solid substrate having a surface and a plurality of optically clear, three-dimensional hydrogel cells attached to that surface at discrete locations. In view of the fact that both of the

references are clearly deficient in this respect, it is submitted that amended claim 1, 18, 31 and 41, which contain these recitations, cannot fairly be said to be obvious from a combination of the two of them, because even if one were to use the foam taught by Hartdegen et al. on the Sundberg et al. device (for which no true motivation has been shown), one would not arrive at the claimed subject matter. Furthermore, the Examiner's mention of the desirability of a long service life is of absolutely no interest in the claimed biochip which, by its nature, has one-shot usage.

Although in the communication filed 26 July 2005 Applicants submitted that claims 1-7 and 9-17, as well as claim 18, would be readable on the elected species, the Examiner telephonically requested a further election of species from the standpoint of an intermediate agent. Applicants elected nitrilotriacetic acid as the species to be elected. However, because this further election was requested telephonically, Applicants did not have the opportunity to submit a claim to this species, which has now been done in the form of new claim 43. The Examiner cited no prior art with respect to the elected species in this environment.

It is believed that the Examiner also meant to indicate that claim 11 was withdrawn from further consideration as being drawn to a nonelected species, as this claim was not listed in any of the rejections specifically set forth. Accordingly, this claim is also treated as being considered withdrawn.

Contemporaneously with the filing of this paper, Applicants are filing a Terminal Disclaimer which should obviate the basis upon which claims 1-7 were rejected.

In view of the foregoing amendments and remarks, and in view of the filing of this Terminal Disclaimer, it is believed that independent claims 1, 18, 31 and 41 are

allowable over the cited references, and that these claims and the claims dependent thereupon should now be allowed, in the absence of any more pertinent prior art. Commensurate with the allowance of such product claims, it is further believed that the pending claims withdrawn from consideration should be rejoined, and all of the claims remaining in this application should now be allowed. It is accordingly believed that issuance of a Notice of Allowance is in order, and such action is courteously solicited.

Should the Examiner believe that any semantic difficulties remain with the claim language, he is invited to telephone the undersigned at the number set forth hereinbelow, who pledges to make an honest effort to resolve any such difficulties that the Examiner might perceive.

Respectfully submitted,

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